18

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,765	05/23/2001	Zhen-Gang Wang	9373/1H812US2	9136

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EXAMINER	
ZHOU, SHUBO	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,765	WANG ET AL.	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,28-39 and 151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 28-39, 151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment and request for reconsideration in the communication filed on 10/20/04, is acknowledged and the amendments entered. Claims 1-24, 28-39, and 151 are currently pending and under consideration.

2. Applicant's arguments in response to the previous Office action have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn. The following rejections and/or objections are reiterated from the previous Office action, mailed 4/20/04, and constitute the complete set presently being applied to the instant application.

3. The objections to the specification in the previous Office action are hereby withdrawn in view of the amendments made to the Title and the Abstract filed 10/24/04.

4. The rejections of Claims 2-3, 5, 10, 19-21, 24, 34-35, and 38-39 under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are hereby withdrawn in view of the amendments to the claims filed 10/24/04.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-18, 28-33, 36-37, and 151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogarad et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 96, pages 2591-2595, 1999) in view of Panchenko et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 93, pages 2008-2013, 1996).

Claims 1-18, 28-33, 36-37, and 151 are drawn to methods and computer systems for selecting a crossover location in a biopolymer sequence for recombination.

Bogarad et al. disclose a method for protein or nucleic acid molecular evolution by recombination and mutagenesis. The method comprises, inter alia, shuffling or swapping structures of folding or domains among different sequences. See page 2592 and Figure 1. Such swapping is interpreted as recombination. The method also comprises generating a plurality of different mutant sequences, which is interpreted as being the data structure of the instant claims, and applying energy function as selection criteria for identifying optimal sequences. The energy function includes secondary

structure subdomain energies and subdomain-subdomain interaction energies. The energy function also considers amino acid side chain interactions. See page 2591, right column, and page 2592, left column. Bogarad et al., however, do not explicitly teach how the sites or locations of the domains or structures for swapping/recombination, i.e. the boundaries of the swapped structures or domains, are selected.

Panchenko et al. disclose a method and computer algorithm for identifying the boundaries of folding structures, referred to as foldons in a protein sequence. The method employs an energy function defined as Θ, which is a measure of relative foldability of protein segments. Such a folding of protein segments is interpreted as comprising coupling interactions of amino acid residues in the segments to form the folded structure. See page 2009. The method of identifying foldon boundaries comprises cutting a polypeptide chain after a certain residue j, and calculating the average Θ value of N-terminal (from the first residue to residue j) and C-terminal (from residue j to the last residue). Then the cleavage point is moved along the chain one residue a time and the average Θ value is calculated. The position of the first residue where a local maximum of Θ is obtained is the boundary of the first foldon. Any average Θ value below this maximun means weakened interactions between units. See page 2009. A higher . indicates higher foldability of segments, i.e. interactions, and it is interpreted as having a lower disruption of the foldon. Further, every sequence resulted from cleavage at a certain residue is interpreted as a crossover mutant. Panchenko et al. state that foldons correlate well with structural modules/domains, which can fold

independently, can be rearranged through genetic engineering, and in some cases have been shuffled during natural recombination. See page 2008.

One of ordinary skill in the art would have been motivated by Panchenko et al. to modify the method of Bogarad et al. to use the method by panchenko for identifying the boundaries of foldons or domains in order to determine precisely the crossover locations for recombination of multiple sequences to achieve finer control for the recombination process.

As to the claims that require that coupling interactions among residues be identified by coupling matrix, absent a clear definition for the phrase in the specification, Fig. 1 of Panchenko et al. is interpreted as being a coupling matrix because it shows the foldability values, i.e. the values for interaction of residues to form a folded structure, for each linear residue of a polypeptide sequence.

As to the claims that require different values for the threshold for the crossover disruption, i.e. the Θ value by Panchenko et al., since different foldons have different Θ values depending on the sequence, as shown in Fig. 1 of Panchenko et al., it would have been obvious to one of ordinary skill in the art that for different sequences and depending on the particular parent sequences and the particular sequences to be created through recombination, different thresholds for the Θ value would have been used.

Applicant's arguments filed 10/24/04 have been fully considered but they are not persuasive.

Applicants first argue that Bogarad does not determine the crossover location by alignment of a plurality of biopolymers prior to recombination but instead utilizes a library of exon pools to make an array of sequences and utilizes an energy function to determine which combination of pool exons has the lowest evolved energy after shuffling and swapping of codons. This is not found persuasive because determining the crossover location by alignment of a plurality of biopolymers prior to recombination is not required in the claims.

Applicants then argue that nowhere does Panchenko describe the foldon interactions between a plurality of biopolymers. This is not found persuasive because again this is not a limitation required in the claims. The claims do not explicitly require that the coupling interactions are among different polymers. On the contrary, claim 1 requires "identifying coupling interactions between pairs of residues in the first polmer sequence". A foldon represents coupling interactions among residues of at least one polymer sequence.

Applicants then argue that there would no reasonable expectation of success of combining the cited references. This is also not found persuasive because both Bogarad and Panchenko provide detailed procedures for their methods, and there would be a reasonable expectation of success for one of ordinary skill in the art to modify the method of Gogarad to use the method by panchenko for identifying the boundaries of foldons or domains in order to determine precisely the crossover locations for recombination of multiple sequences to achieve finer control for the recombination process.

7. Claims 19-24, 34-35, 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogarad et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 96, pages 2591-2595, 1999) in view of Panchenko et al. (IDS document: Proc. Natl. Acad. Sci. USA, Vol. 93, pages 2008-2013, 1996), as applied to claims 1-18, 28-33, 36-37, 40, and 151 above, further in view of Jonsson et al. (Nucleic Acids Research, Vol. 21, pages 733-739, 1993).

Claims 19-24, 34-35, 38-39 are drawn to methods and computer systems executing the methods for selecting a crossover location for recombination.

As applied to claims 1-18, 28-33, 36-37, and 151 above, Bogarad et al. and Panchenko et al. disclose methods and systems for recombination and for determining the boundaries of folding structures, which can be served as crossover locations for recombination. However, Bogarad et al. and Panchenko et al. do not explicitly teach that the crossover mutants are generated by aligning a plurality of polymer sequences, identifying possible cut points and generating crossover mutants.

Jonsson et al. disclose a method of creating new promoter structures using a quantitative sequence-activity model (QSAM). Jonsson et al. aligned 25 promoter sequences, analyze the strength of each residue relative to the overall promoter strength and identified two new sequences based on the alignments and strength analysis. See page 734, Table 1, and page 736, Figs 1-3. The new sequences created PLS1 and PLS2 have the highest promoter activity. While Jonsson et al. do not explicitly recite the term recombination, it would have been obvious to one of ordinary skill in the

art that the new promoter sequences predicted, PLS1 and PLS2, are produced, in silico, by recombining the 25 parental sequences through crossovers (see Table 1), and these are considered as crossover mutants. Laboratory tests show that PLS1 and PLS2 exhibits higher biological activity than all the 25 parental sequences.

One of ordinary skill in the art would have been motivated by Jonsson et al. to modify Bogarad et al. and Panchenko et al. to use sequence alignments coupled with strength analysis, to find crossover mutants that would have the highest biological activity.

Applicant's arguments filed 10/24/04 have been fully considered but they are not persuasive.

Applicants argue that Jonsson does not determine the location of cutpoints for a crossover mutation between a plurality of biopolymers but instead looks at each base separately and determines which base out of the group represents the lowest energy from a matrix and generates a synthetic sequence base by base. This is not found persuasive because Table 1 on page 734 clearly align multiple polymer sequences and list the recombinant sequences at the bottom. The alignments of the parental sequences and recombinant sequences in Table 1 would have made it obvious of the cutpoints for the crossovers to one of ordinary skill in the art.

Double Patenting

8. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or

discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9. Claims 1-24, 28-39, and 151 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-24, 28-39, and 151 of US copending application 10/016,668, filed 10/26/01. This is a provisional double patenting rejection. The invention in every one of claims 1-24, 28-39, and 151 of the instant application is identical in scope compared to the corresponding claims of 1-24, 28-39, and 151 of US copending application 10/016,668. Even the wordings are identical.

In response to the provisional double patenting, applicants state that "applicants agree to cancel claims 1-24, 28-39, and 151 in the copending '688 application". However, this is not considered an official amendment to application 10/016,688 because this is a response filed for application 09/863765. This provisional application is thus retained.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.**

12. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of

document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.
Patent Examiner

J.S. Brusca 10 January 2005
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER